Remarks

Introduction

Claims 1-23 were pending. By way of this response, claims 1, 7, 17, 20, and 21 have been amended, and claim 23 has been cancelled without prejudice. Support for the amendments to the claims can be found in the application as originally filed, and no new matter has been added. Accordingly, claims 1-22 are currently pending.

Claim Objections

Claim 7 has been objected to for lack of antecedence for the term "effect".

Claim 7, which depends from claim 1, has been amended to render the rejection moot.

In view of the above, applicant submits that the objection to claim 7 has been overcome.

Obviousness-type Double Patenting

Claims 1-5, 7-12, 17-18, and 20 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 and 5-12 of U.S. Application No. 10/421,504, which is directed to methods of treating epilepsy. Claim 23 has been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 10-11 of U.S. Pub. No. 2004/0062776, which is directed to treating methods of treating fibromyalgia. Claim 23 has also been provisionally rejected under the judicially

created doctrine of obviousness-type double patenting over claims 1-5 and 10-12 of U.S. Pub. No. 2004/0018213, which is directed to methods of treating pain. Claim 23 has also been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 3-4, and 10-12 of U.S. Pub. No. 2004/0018212, which is directed to methods of treating pain. Claims 1-5, 7-12, 17-18, and 20 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 and 5-13 of U.S. Pat. No. 6,620,415, which is directed to methods of treating Parkinson's disease. Claims 1-5, 17-18, and 20 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 and 5 of U.S. Pat. No. 6,372,226, which is directed to methods of treating pain. Claims 1-5, 17-18, and 20 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3 and 13 of U.S. Pat. No. 6,333,037, which is directed to methods of treating pain. Claims 1-5, 17-18, and 20 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3, 5, 9-17, and 13 of U.S. Pat. No. 6,306,403, which is directed to methods of treating Parkinson's disease. Claims 1-5, 17-18, and 20 have been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-3, 12-13, 28-29, and 36 of U.S. Pat. No. 6,113,915, which is directed to methods of treating pain. Claim 23 has been rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-32 of U.S. Patent No. 6,623,742, which is directed to methods of treating fibromyalgia.

In short, it appears that the Examiner is basing the provisional and non-provisional obviousness-type double

patenting rejections on the belief that the cited patent publications, applications, or patents claim a species of the genus encompassed by the present claims.

Applicant disagrees with the rejections and traverses the rejections, as they relate to the present claims. In particular, applicant submits that the claims of the cited publications, applications, and patents are not directed to species of the presently claimed genus of neuropsychiatric disorders. For example, the claims directed to epilepsy and Parkinson's disease are methods of treating movement disorders, not neuropsychiatric disorders as recited in the present claims. In addition, fibromyalgia, and pain as recited in the cited references, are not symptoms of neuropsychiatric disorders. In fact, fibromyalgia is a type of pain syndrome.

The present claims are directed to treating neuropsychiatric disorders, such as by alleviating or treating a symptom of a neuropsychiatric disorder. For example, the present claims are directed to alleviating or treating cognitive or mental effects related to a neuropsychiatric disorder, such as schizophrenia. As indicated in the above-identified application, neuropsychiatric disorders affect one or more mental faculties, such as thinking and cognition; mood; social behavior; and learning, memory, and intelligence.

Persons of ordinary skill in the art recognize and understand that movement disorders, such as epilepsy and Parkinson's disease, are neurological conditions that are different and distinct from neuropsychiatric disorders. Similarly, persons of ordinary skill in the art recognize and understand that pain, including fibromyalgia, are not cognitive

or mental issues, and are conditions that are different and distinct from neuropsychiatric disorders.

Applicant submits that a teaching of a method of treating a movement disorder, such as epilepsy or Parkinson's disease, or a method of treating pain, including fibromyalgia, does not render a method of treating a neuropsychiatric disorder obvious to a person of ordinary skill in the art.

In view of the above, including the differences and distinctions between movement disorders and pain set forth in the cited patent publications, applications, and patents, and neuropsychiatric disorders set forth in the present claims, applicant submits that the present obviousness-type double patenting rejections are improper and should be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 1-23 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabling a method of administering any dosage size to any local intracranial region location of a mammal to treat a neuropsychiatric disorder. The Examiner acknowledges that the specification is enabling for a method of alleviating at least one symptom associated with a neuropsychiatric disorder with specific non-toxic doses of a clostridial neurotoxin delivered locally to the site which affects the symptom(s) being alleviated. Applicant traverses this rejection as it pertains to the present claims.

The claims have been amended to the enabling scope as suggested in the Office Action to indicate that the amount of the neurotoxin administered to the intracranial region to treat

a neuropsychiatric disorder is not toxic to the person, e.g., it is a non-lethal amount of neurotoxin. The claims have also been amended to indicate that the neurotoxin is administered to an intracranial region located within the skull of the patient. Thus, applicant submits that the present claims more clearly reflect the amount of neurotoxin administered into the patient, and that the administration is at a specific location.

In view of the above, applicant submits that the claims satisfy the requirements of 35 U.S.C. § 112, first paragraph, and respectfully requests that the rejection of the present claims based on this statutory provision be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 1-5, 7-8, 10, and 12-20 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Binder (U.S. Pat. No. 5,714,468). Claims 1-8 and 10-20 have been rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Aoki et al. (U.S. Pat. No. 6,458,365). Claims 1-4, 7, 9, and 12 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Micheli et al. (1998). Claims 1-5, 7, 12-20, and 23 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Auchus et al. (1995). Claims 1-5, 7, 17-19, and 21-23 have been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Bassitt et al.

The claims have been amended as set forth above to address the rejections under 35 U.S.C. § 112. Applicant traverses the rejections under 35 U.S.C. § 102 as the rejections relate to the present claims.

Applicant submits that none of the cited references disclose, teach, or even suggest administration of a neurotoxin, such as a botulinum toxin, to a patient to treat a neuropsychiatric disorder, as recited in the present claims. In addition, as acknowledged in the Office Action, applicant submits that the cited references only disclose intramuscular administration of a botulinum toxin to treat conditions other than neuropsychiatric disorders. For example, the Office Action acknowledges that Binder teaches intramuscular administration of a botulinum toxin (Office Action page 13, third paragraph). The Office Action states that Aoki et al. discloses administration to the muscles of the head (Office Action page 14, third full paragraph).

Regarding Micheli et al., applicant submits that the administration location of botulinum toxin is not disclosed, and in particular, applicant disagrees with the Examiner that Micheli et al. discloses administration of botulinum toxin to the pontine region. Micheli et al. discloses that a patient developed left periocular muscle twitching, which spread to lower facial muscles. The patient received treatment with botulinum toxin. Micheli et al. does not indicate where the botulinum toxin was administered to the patient. Since, in 1998, it was known that botulinum toxin resulted in therapeutic paralysis of muscles, and since Micheli et al. does not disclose where botulinum toxin was administered to the patient, a person of ordinary skill in the art would readily conclude that the botulinum toxin was administered to a muscular region undergoing twitching, such as the left periocular muscles. See e.g. the three attached articles: Oziekin et al., "Botulinum toxin treatment in hemifacial spasm", Movement Disorders, Vol. 11, Supp. 1 (1996); Carruthers et al., "Botulinum A exotoxin in

clinical ophthalmology", Can. J. Ophthalmol, 31(7):389-400 (1996); and Eleopra et al., "The botulinum toxin treatment of lower facial muscles in patients affected by hemifacial spasm", Mov. Disord., Vol. 13, Supp. 2:224 (1998). The only mention of the pontine region by Micheli et al. is with respect to the speculation that compression of the facial pontine root entry zone may result in hemifacial spasm, which is not a neuropsychiatric disorder.

Applicant submits that Auchus et al. discloses intramuscular injection of botulinum toxin to treat cervical dystonia, as set forth on page 393, first and sixth paragraphs of Auchus et al.. The botulinum toxin was administered to treat a neuromuscular condition, not a neuropsychiatric disorder, as recited in the present claims.

Regarding Bassitt et al. applicant submits that Bassitt et al. also discloses intramuscular injection of botulinum toxin into the eyelids of patient with blepharospasm (uncontrolled blinking). See e.g. page 155, third paragraph of Bassitt et al.. The patient was not administered botulinum toxin to treat a neuropsychiatric disorder, or a symptom thereof, as recited in the present claims.

Applicant submits that none of the cited references disclose, teach, or suggest the present invention. For example, the cited references do not disclose, teach, or even suggest local administration of a Clostridial neurotoxin to neural tissue at an intracranial site within the skull of the patient to treat or alleviate a symptom of a neuropsychiatric disorder, as recited in the present claims.

In contrast, each of the cited references (Binder, Aoki et al., Micheli et al., Auchus et al., and Bassitt et al.) disclose administration of a botulinum toxin outside of the skull, such as to a muscle located outside of the skull. The references do not disclose, teach, or even suggest administration of a Clostridial neurotoxin to neural tissue, and furthermore, do not disclose, teach, or even suggest administration of a Clostridial neurotoxin to neural tissue at an intracranial site located within the skull of the patient, let alone to do so and treat a neuropsychiatric disorder of the patient.

Because the cited references do not disclose each and every limitation recited in the present claims, applicant submits that the present claims cannot be properly anticipated by the references under 35 U.S.C. § 102. In addition, applicant disagrees that any of the references inherently disclose the subject matter of the present claims. To the extent that the Examiner maintains the inherency position, applicant requests the Examiner to provide evidence substantiating the inherent disclosure of the references.

In view of the above, applicant submits that the present claims, that is claims 1-22, are not anticipated by Binder, Aoki et al., Micheli et al., Auchus, et al, or Bassitt et al., under 35 U.S.C. § 102, and that the present claims are unobvious from and patentable over Binder, Aoki et al., Micheli et al., Auchus, et al, or Bassitt et al., taken alone or in any combination, under 35 U.S.C. § 103.

In addition, each of the present dependent claims is separately patentable over the prior art. For example, none of the prior art disclose, teach, or even suggest the present

methods including the additional feature or features recited in any of the present dependent claims. Therefore, applicant submits that each of the present claims is separately patentable over the prior art.

Conclusion

In conclusion, applicant has shown that the present claims are not subject to rejection for double patenting, satisfy the requirements of 35 U.S.C. § 112, and are not anticipated by and are unobvious from and patentable over the prior art under 35 U.S.C. §§ 102 and 103. Therefore, applicant submits that the present claims, that is claims 1-22 are allowable. Therefore, applicant respectfully requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, the Examiner is requested to call (collect) applicant's attorney at the telephone number given below.

Date: 10/19/04

Respectfully submitted,

Frank J. Uxa
Attorney for Applicant
Under 37 CFR 1.34(a)
Registration No. 25,612
4 Venture, Suite 300
Irvine, California 92618
(949) 450-1750
(949) 450-1764 Facsimile

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P827

BOTULINUM TOXIN TREATMENT IN HEMIFACIAL SPASM

M.F Öztekin*, N. Öztekin
SSK Ankara Hospital Department of Neurolgy.
(Ankara, TURKEY)

Hemifacial spasm (HFS) is a periodic contraction of the musculature of one side of the face. It occurs in adults, mostly women and may be accompanied by mild ipsilateral facial weakness. Herein we report the results of 58 hemifacial spasm patients treated with local botulinum toxin type A injections. The patients had injections of botulinum toxin into 5 periocular sites and two sites on the cheek, and each injection consisted of 2.5 units of toxin. The mean age was 63 years (range 40-79) and the mean duration of HFS was 7.8 years (range 0.5 - 13 years). The patients were followed up 31 months with clinical examination and video recordings. The mean onset of the effect was 12 days and lasted mean 10 weeks. No complications were observed except temporary ptosis in 8 patients. In 21 patients whe had repeated injections for more than 26 months the mean onset of the effect of the toxin delayed and was observed after mean 31 days.

Despite the minor complications and the temporary nature of the relief of symptoms the results of the treatment were satisfactory. In conclusion botulinum toxin A injection is a valid alternative in the treatment of HFS patients.

Movement Disorders, Vol. 11, Supplement 1, 1996

Mov Disord 1996;11(Suppl-
Abstract P827):219

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INTERPRETING TECHNOLOGY

Botulinum A exotoxin in clinical ophthalmology

Jean D.A. Carruthers,* MD; Alastair Carruthers,† MD

Two centuries ago in Germany clinical botulism was recognized as an entity. The disorder was called botulism because sausages (*botulus* in Latin) were found to be a source of infection. Recognizing this, Virchow, the famous 19th century pathologist, once offered to duel with sausages.[1] The anaerobic bacterium causing the outbreaks was first characterized at the end of the last century. Van Ermengem[2] initially called the organism *Bacillus botulinus*, but at an international nomenclature conference held in 1922 its name was changed to *Clostridium botulinum* to acknowledge both its spindle shape (*klōstēr* is Greek for "spindle") and its anaerobic metabolism (bacilli were by definition aerobes).

The toxin produced is called an exotoxin because it is liberated in culture from the intact bacterium. There are eight toxins described: types A, B, C, C^2, D, E, F and G. Types A, B and E are most commonly associated with clinical botulism in humans.[3] Type A is the type used most widely in clinical medicine and is the only type available commercially. Types B and F are under investigation in experimental drug trials[4,5] and are being studied for use in patients with an antibody response to type A.[6]

The current therapeutic use of botulinum A exotoxin in ophthalmology and other disciplines is the direct result of the pioneering work of Dr. Alan Scott,[7] who wished to find a pharmacologic way to treat strabismus. In 1982 he directed a multicentre trial of 292 investigations from 28 countries. A total of 5728 patients with strabismus, 9983 with essential blepharospasm and 3871 with hemifacial spasm were safely and effectively treated with the toxin. In 1989 the toxin was approved by the United States Food and Drug Administration for use in blepharospasm, hemifacial spasm and strabismus in adults and children aged 12 years or more. In the same year the American Academy of Ophthalmology issued its position statement in support of the therapeutic use of botulinum A toxin.[8]

The clinical use of botulinum toxin has been well explored and documented worldwide over the past 15 years. Botulinum toxin chemodenervation is an alternative to incisional strabismus surgery, particularly in patients with recent onset of third or sixth cranial nerve paresis and those with small-angle strabismus (such as residual strabismus after surgery).[9] It reduces the amplitude and intensity of nystagmus and thus improves visual acuity and decreases oscillopsia.[10] In blepharospasm, hemifacial spasm, Gilles de la Tourette's syndrome, facial asymmetry and eyelid facial nerve synkinesis, treatment is exact enough to weaken overactive muscles without causing complete paresis. Deliberate injection into the levator muscle can induce protective ptosis (Fig. 1).

The newest application of the toxin is in the area of facial aesthetics, to smooth deep muscle-induced facial grooves, such as glabellar furrows, periocular crow's-feet and horizontal forehead lines.[11]

Pharmacokinetics

The toxic portion of the botulinum A toxin molecule is a long polypeptide chain with two disulfide bonds (Fig. 2). Cleavage at a disulfide bond results in a heavy chain with a molecular weight of

Fig. 1—Protective ptosis induced by deliberate chemodenervation of levator palpebrae superioris.

*Clinical professor, Department of Ophthalmology, University of British Columbia, Vancouver, BC

†Clinical professor, Division of Dermatology, University of British Columbia, Vancouver, BC

Reprint requests to: Dr. Jean D.A. Carruthers, 943 West Broadway, Suite 720, Vancouver BC V5Z 4E1

Can J Ophthalmol
1996;31(7):389-400.

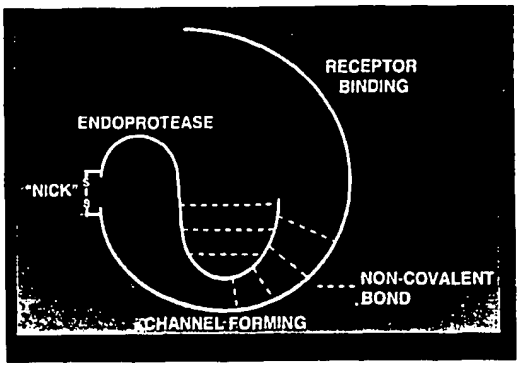

Fig. 2—Schematic drawing of toxic portion of botulinum A exotoxin molecule. Cleavage at disulfide bond produces conformational change in molecule that markedly increases potency of toxin.

100 000 Da and a light chain with a molecular weight of 50 000 Da. The cleavage causes a change in molecular conformation, which markedly increases the potency of the toxin. In bacterial cell culture medium the cleaved molecule (molecular weight 150 000 Da) links up with approximately equal sized molecules of hemagglutinin and "nontoxic molecule." The latter is believed to stabilize the botulinum toxin molecule in the gastrointestinal tract, and the former, to encourage development of an anaerobic environment to allow the organism to proliferate.[12]

The three molecules together make a 450 000-Da subunit that links up with another such unit, for a combined molecular weight of 900 000 Da.

The heavy chain binds the molecule to the presynaptic neuron and causes channels to form to allow the whole molecule to enter the cell. The light chain acts as a zinc-dependent metalloendoprotease that inhibits release of acetylcholine packets from the presynaptic neuron.[12]

Four steps are required to halt release of acetylcholine packets from the presynaptic neuron.[13,14] First, toxin binding to the presynaptic neuron takes 32 to 64 minutes in the mouse hemidiaphragm model. The second step, in which the botulinum A toxin molecule is drawn within the confines of the cell, is energy dependent. Once the molecule is inside the cell, the vesicle containing the molecule is lysed, and in some manner not yet fully understood the botulinum toxin short chain inhibits acetylcholine packet release.

Thus, botulinum A toxin does not interfere with the transmission of the nerve impulse but, rather, its final transmission across the myoneural junction. The muscle weakness usually begins 48 to 72 hours after injection, but some patients may not show maximum weakness for 7 to 14 days after injection.[15] Retreatments should not be given during this interval.

Toxicity

The toxicity of botulinum A toxin is expressed in biologic mouse units rather than nanograms because a proportion of toxin in each vial is nontoxic. An enzyme-linked immunosorbent assay would thus give an exaggerated report of vial toxin content. One mouse unit is the amount of toxin that would kill 50% (LD_{50}) of a group of female Swiss Webster mice weighing 18 to 20 g each.[16] The estimated human LD_{50} for a 70-kg person is 40 units/kg, or 2500 to 3000 units.[17,18] The usual therapeutic dosage for ophthalmic indications is 2.5 to 100 units (0.08% to 3.3% of the LD_{50}), a substantial and reassuring dosage margin.

Histopathological changes in denervated muscle

Histopathological changes in denervated striated muscle from animal models and human orbicularis oculi (from blepharoplasty specimens) are striking and characteristic.[19] After 2 weeks there is diffuse muscle atrophy, which continues for a further month and then stabilizes. These changes are parallelled by a quantitative change in the pattern of acetylcholinesterase staining. Normally the stain is taken up only at the myoneural junction, but after injection of botulinum A toxin the stain takes over most of the sarcolemma. After 4 to 5 months the stain is again seen only at the myoneural junction.

The normal neuromuscular junction is in a constant flux of regeneration, repair and renewal, with new axonal sprouts and new end plates joining, and old neuromuscular junctions are reabsorbed.[20] The application of botulinum A toxin amplifies this normal process, and the effect is seen within 10 days of injection.[20] New axonal sprouts are nonmyelinated and spring from both sides of the neuromuscular junction. The toxin enhances neuromuscular junction repair and remodelling for 3 to 6 months, but continued axonal sprouting has been reported 3 years after treatment.[21]

Immunology

Botulinum toxin is an immunogenic protein. Antibodies have been reported in patients who have

received 100 to 1200 units per session.[22] They have not been documented at doses under 50 units and to our knowledge have never been reported in patients treated for ophthalmologic or aesthetic indications. Risk factors for antibody formation are injection of more than 100 units per session and retreatment within 1 month of initial injection.[23]

Commercial toxin preparation, toxin stability and reconstituting toxin for clinical use

In Madison, Wis., in 1979 Dr. E.J. Schantz prepared 150 mg of purified botulinum A exotoxin. The 100 mg he gave to Dr. Alan Scott is the same batch now available commercially from Allergan Inc., Markham, Ont. It is this single batch that has been approved for use in humans by the Food and Drug Administration in the United States and the Health Protection Branch in Canada.[24]

The specific toxicity of this batch is 3×10^7 mouse units plus or minus 20% per milligram of protein. It is stored at -4°C in a buffered suspension at pH 6.8 and has been stable since its initial preparation.[25]

US Food and Drug Administration regulations demand a release specification of 100 ± 30 units per vial. Allergan provides 100 ± 10 units per vial. A recent study of the toxicity of four vials showed 127 ± 10 units per vial.[26]

For practical clinical use we assume each vial to contain 100 units of toxin in lyophilized form. The physician adds sterile saline without preservative to give the desired concentration. For strabismus and nystagmus 1.0 mL is added to give a concentration of 5 units in 0.05 mL.

The toxin is best used on the day it is diluted because after 12 hours there is a loss of toxicity of 43.9%.[27] If the unused diluted toxin is refrozen there is a loss of toxicity of 70% at both 1 week and 2 weeks. However, clinical observations have not correlated with this, and some physicians keep the diluted toxin refrigerated for as long as a month.[28] We caution that since there is no preservative in the saline, bacterial contamination would be a possible complication.

When diluting the toxin before use, it is important to let the saline bubble gently into the vial rather than allowing the vacuum in the vial to draw the saline in with force, causing bubbling and surface denaturation. Allergan supplies a videotape demonstrating the correct mixing procedure.

Ophthalmologic indications

Strabismus

The extraocular muscles function in power-balanced pairs. If one member of a muscle pair becomes weaker, its partner muscle (ipsilateral direct opponent) will undergo sarcomere shortening or muscle contracture and will pull the eye toward its own unopposed field of action.

Botulinum toxin can be used to create a new extraocular muscle imbalance that will correct strabismus.[29] For example, if a patient presents with esotropia, injection of toxin into the ipsilateral medial rectus will allow the sarcomeric shortening in the lateral rectus to pull the eye to a straightened position. The net effect is equivalent to surgically recessing the muscle and resecting its ipsilateral antagonist, as with the "recess–resect" incisional strabismus procedure. However, in adults with strabismus botulinum toxin chemodenervation is performed under topical anesthesia with electromyographic control in the clinic setting rather than under general anesthesia in the hospital operating room.

Paretic strabismus

To determine whether a muscle palsy is restrictive or paretic, botulinum toxin is injected into the ipsilateral antagonist of an apparently paretic muscle. This allows any spontaneous recovery of the weak muscle to be assessed.[30] In many instances this diagnostic test may also be therapeutic, thus obviating the need for incisional surgery.

Sixth cranial nerve paresis

Acute: Botulinum A toxin injection into the ipsilateral contracting medial rectus within several weeks of the onset of lateral rectus palsy is now considered appropriate.[31] It restores the patient's binocularity in primary gaze and reduces the eccentricity and discomfort of the head turn.[31–33]

The effect is particularly helpful symptomatically to the patient in the 6 months after the onset of the palsy. Botulinum toxin injection does not enhance lateral rectus reinnervation and recovery.[34] Injection of toxin or conventional adjustable-suture surgery can be used to maintain alignment.

Bilateral sixth nerve paresis does not respond as well as unilateral sixth nerve paresis to botulinum

toxin treatment, possibly because the prognosis is less favourable in bilateral cases in general and because bilateral cases are often due to injury.

Chronic: It may be difficult to control nonrecovering sixth nerve paresis with botulinum toxin treatment alone.[35] However, Repka and colleagues[36] used the drug in a heterogeneous group of patients with chronic sixth nerve paresis and found that the disorder could be controlled with the use of the toxin alone in 41% of cases.

Anterior segment ischemia is more frequent with increasing number of muscles operated and increasing age of the patient.[37] The Hummelsheim and Jensen procedures may disrupt vascular supply to the anterior segment. Combining transposition surgery with botulinum toxin treatment to the ipsilateral medial rectus can successfully give a mean diplopia-free field of 51%.[38] Keech and associates[39] reported anterior segment ischemia in one case in which two-muscle transposition surgery was combined with botulinum toxin injection to the medial rectus, a combination previously felt to carry no risk to the vascular supply.[38]

Third cranial nerve paresis

Spontaneous recovery from third nerve paresis may be slower than recovery from sixth nerve paresis. In addition, recovery may be masked by ipsilateral rectus contracture and complicated by associated vertical strabismus due to asymmetric involvement of the vertical recti and inferior oblique. Botulinum toxin injection to the lateral rectus may be effective, but several injection sessions may be necessary.[40]

Fourth cranial nerve paresis

There are insufficient data to analyse the response of fourth nerve paresis to botulinum toxin treatment.

Nonparetic strabismus

Horizontal deviations

Postoperative under- and overcorrection: The small residual angle after incisional strabismus repair is one of the most successful applications of botulinum toxin[41] because it extends the "window of adjustment"[42] for both horizontal and vertical under- and overcorrection.

Sensory heterotropia: Sensory heterotropias are inherently unstable and often drift after surgery. Rather than using repeated surgical procedures, the eye can be realigned as necessary every 6 months with botulinum toxin, without creating new scar tissue. In patients with phthisis and strabismus the drug should not threaten the vulnerable anterior segment circulation.

Strabismus after retinal detachment repair: A total of 60%[43] to 75%[44] of patients with strabismus after retinal detachment repair can be helped with botulinum toxin alone. The advantages are that the drug does not disturb retinal explants and carries less risk for anterior segment ischemia.

Comitant horizontal deviations: Horizontal misalignment responds with a percent net effect between 60% and 70% at 6 months.[45] Esotropia responds better than exotropia in both adults and children.[40] Smaller deviations (20 prism dioptres or less) respond better than larger deviations.[41,46]

Infantile esotropia: Botulinum toxin treatment can be given while the infant's visual sensorimotor system is still developing.[47] There are no prospective studies comparing the results of very early (before 6 months) conventional incisional surgery (with bimedial recession) with botulinum toxin therapy in infants and children. However, a long-term study showed considerable motor and sensory stability in large cohorts of children treated with the drug.[48]

Vertical deviations

Nonrestrictive:

• Dissociated vertical deviation: Dissociated vertical deviation can be treated with injection of either the ipsilateral superior rectus or the contralateral inferior rectus. Both approaches are effective, although the former is nearly always associated with transient ptosis.[49]

Restrictive:

• Dysthyroid ophthalmopathy: In the acute inflammatory phase of dysthyroid ophthalmopathy the muscles may be unsuitable for surgery, but the patient is still struggling to maintain or to reestablish single binocular vision over a relatively small angle. Botulinum toxin helps change alignment[50] before intramuscular fibrosis develops.[51] The drug can safely be administered well before incisional adjustable-suture strabismus surgery can be carried out.

• Superior rectus contracture secondary to fourth cranial nerve paresis: Superior rectus injections are effective in treating superior rectus contracture secondary to fourth nerve paresis,[49] but the patient may

prefer adjustable-suture recession because of the virtually 100% likelihood of ipsilateral ptosis with botulinum toxin. This appears within 2 weeks of the injection and usually persists for 4 to 5 weeks.

Nystagmus

Nystagmus responds to injections into the retrobulbar space[52] or directly into the rectus muscles.[10] Retreatment (every 3 to 6 months) is the norm. Botulinum toxin allows the amplitude of oscillation to be damped and the effort to see to be decreased, with resulting improved visual acuity. In our experience retrobulbar injections are best for multidirectional nystagmus, particularly in brain-injured adult patients who have oscillopsia. Direct horizontal rectus injections are effective in treating uniplanar horizontal jerk or pendular nystagmus, most commonly seen in patients with congenital nystagmus.

Care after injections for strabismus and nystagmus

The peripheral retina should be examined with the indirect ophthalmoscope to ensure there is no perforation or hemorrhage. A broad-spectrum antibiotic drop is instilled into the conjunctival sac. The patient is instructed to remain upright for 4 hours after the injection to facilitate binding of the toxin to the extraocular muscle chosen rather than to susceptible adjacent muscles, such as the levator palpebrae superioris or other horizontal recti. The patient is informed that the toxin starts to work 24 to 72 hours after injection and that the full paretic effect lasts approximately 8 to 12 weeks.

Blepharospasm

So-called "benign" essential blepharospasm creeps up on affected patients over several years. Initially they may notice only increased blinking, which is easily tolerated and is not embarrassing. As time goes on the blinking is joined by involuntary spasms of orbicularis contraction, such that the lids may close suddenly when the patient is driving, crossing the street or reading or during social interactions. The eyelid closure is complete and sustained. Some people discover "tricks," usually involving proprioceptive signals, such as touching the cheek, pursing the lips or whistling, that allow the orbicularis to relax. Gradually, these manoeuvres fail, and the person ceases being able to read, drive and work and starts to curtail activities outside the home.[53,54] The condition was previously thought to be rare because these people are functional shut-ins (although their eyes may be capable of 20/20 vision).

Before the introduction of botulinum toxin, surgical techniques such as facial nerve section and extirpation[55] and orbicularis oculi stripping[56] were used to treat the condition. Overall, 50% of patients treated with the former procedure showed a recurrence within 2 years,[55] and with the latter procedure eyes were lost as a result of exposure keratitis and other related problems.[56]

In 1980 Scott[7] recognized to potential of botulinum toxin in managing this condition. Injections in several sites (Fig. 3) allow the lids to function almost normally for several months at a time.[9] Patients are able to return to the workforce and resume their normal social and professional activities.

The starting dose is 20 units per side in patients aged 30 to 50 years and in men over the age of 50; in women over 50 years the starting dose is 15 units (as these women may have smaller muscles). It is safer, particularly in less robust patients, to start with a lower dosage and treat again as necessary. The dosage is increased by 5 units per side, with at least 1 month between injection sessions. The effect usually lasts 3 to 4 months, but some patients will require treatment every 8 weeks and others every 6 months. Patients become sophisticated toxin "consumers" and will inform you about which injection sites "need more" and whether the total dose was adequate for their needs.

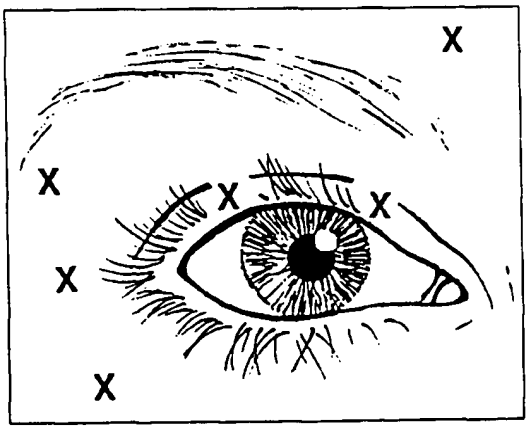

Fig. 3—Injection sites for "benign" essential blepharospasm. Injection in pretarsal orbicularis reduces incidence of iatrogenic ptosis.

Between July 1, 1983, and July 31, 1995, one of us (J.D.A.C.) treated 612 patients with blepharospasm with botulinum A toxin in 4735 injection sessions (10 injection sites per session). Some patients have now had over 60 injection sessions. All patients experience trepidation at the return of their spasms, and all say that their active lives would not be possible without the treatment. Three patients have experienced spontaneous remission of their spasms. All have mild residual spasms when they are stressed or fatigued but are otherwise able to carry on normal lives.

Hemifacial spasm

Patients with hemifacial spasm have a chronic repeated twitch on one side of the face, sometimes localized to the periocular region but more commonly involving the entire hemiface.[57] Most cases are unilateral. The involuntary spasm may initially localize to the orbicularis oculi but later spreads to involve all the lower muscles of facial expression. The mouth and cheek are pulled toward the affected side, deepening the melolabial fold and resulting in muscular hypertrophy on that side. The problem worsens when the patient lies down to sleep.

The expressive and protective subcutaneous musculature of each hemiface is innervated by its ipsilateral seventh cranial nerve. In patients with hemifacial spasm this nerve fires almost continuously under stimulation by an anomalous vascular loop of the basilar or posterior inferior cerebellar artery or by a congenital localized vascular malformation. Less than 1% of patients have a posterior fossa neoplasm.[58] Neuroimaging is usually done on initial presentation to make this distinction. It is presumed that the constant abrasion of the myelin sheath of the intracranial seventh nerve by the vascular loop is the cause of the clonic discharge. The resulting demyelination may make the nerve more sensitive to the effects of botulinum toxin, so that these patients need injections less often than those with essential blepharospasm.

Injections throughout the hemiface are needed to control the ipsilateral spasms[57] (Fig. 4). The pattern for the orbicularis oculi is the same as for blepharospasm. The superficial anatomic landmarks for the involved lower facial muscles, the zygomaticus major and minor and the risorius, can be influenced with an injection halfway down an imaginary vertical line connecting the external canthus of the eye and the external angle of the mouth. A small dose (e.g., 2.5 units) is appropriate for these highly sensitive lower facial muscles; the effect with bigger doses will mimic facial palsy. An injection of 2.5 units is given to the masseter 2.5 cm temporal to the zygomaticus site. Injections are never administered medial to the modiolus, even if the patient requests it, because the orbicularis oris will become incompetent. The injections are given relatively superficially because deeper injection will paralyze the buccinator, and the patient will catch the cheek in the teeth as he or she chews. The effect usually lasts 4 months, sometimes longer.

Complications

The main complication of the noncosmetic use of botulinum toxin is iatrogenic ptosis. Initially we injected the orbital (preseptal) portion of the upper eyelid, aiming the needle medially and laterally, away from the central portion of the levator. We had very high ptosis rates of 30% to 50%. Subsequently, by injecting below the superior tarsal fold and avoiding the levator as well as asking the patient to remain upright for 4 hours after the injection session, the ptosis rate was reduced to just over 2%.[59]

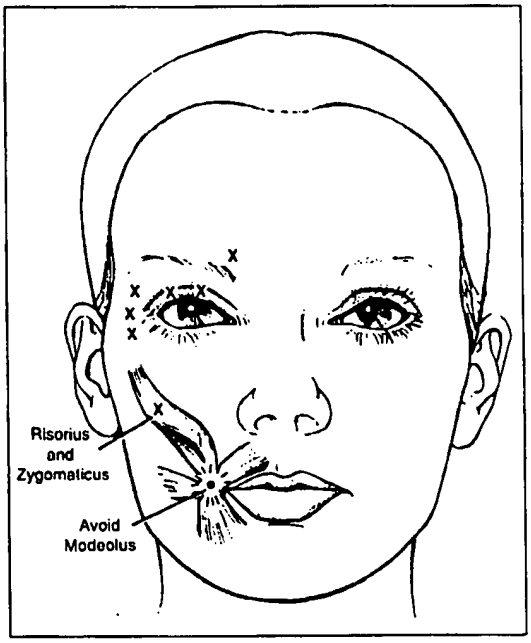

Fig. 4—Injection sites for hemifacial spasm. Note additional lower facial injection sites in zygomaticus and levator labii superioris aleque nasi. It is important to respect muscle function within modiolus so as to preserve competence of orbicularis oris.

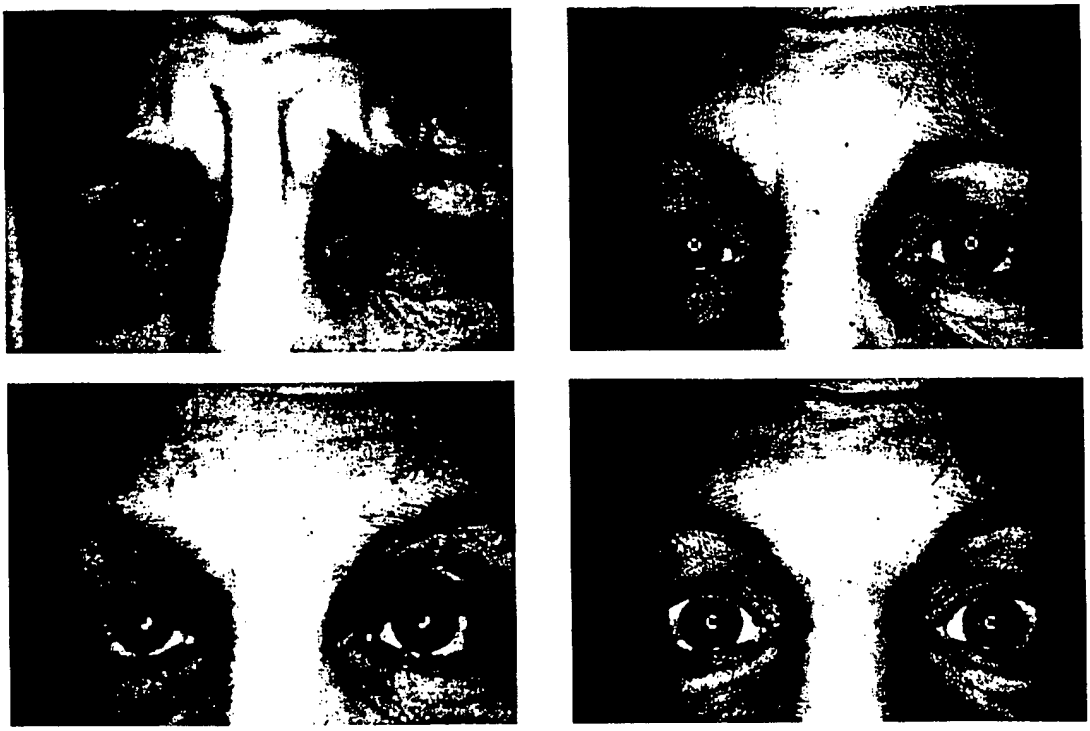

Fig. 5—Left: Pretreatment appearance of deep glabellar furrows, with patient's face frowning and at rest. Right: Corresponding photographs 1 week after treatment of glabellar region and orbicularis oculi with 25 units of botulinum A toxin.

The ptosis is always reversible, lasting an average of 4 weeks. The patient may need reassurance during the recovery process.

Patients receiving prophylactic acetylsalicylic acid (ASA) therapy should hold an ice pack to the treated area before and after treatment to reduce bruising.

The injections themselves are mildly uncomfortable for some patients and just off comfortable for others. The discomfort relates to the needle and remits when the needle is withdrawn. We use a 30-gauge needle on a tuberculin syringe rather than a swaged-needle insulin syringe so that we can draw the toxin up through the thick rubber cap with a 19-gauge needle, keeping the 30-gauge needle in pristine sharpness for the patient.

If large doses are given in the lower lid temporary ectropion may result. All starting dosages should be conservative until the individual patient's response can be observed. It is always possible to retreat in a month if the response is not adequate.

There have been no systemic reactions in our patients in 14 years of use.

Cosmetic indications

Facial lines and wrinkles are perceived to be a "natural" result of aging. Three factors are primarily responsible for this alteration from the previously youthful appearance: aging (intrinsic and sun-related), gravity (vertical and sleep lines) and muscular action (the muscles of facial expression are connected to the overlying facial skin by the subcutaneous muscular aponeurotic system).

Glabellar (brow) furrows

In people who habitually frown when concentrating, deep vertical lines develop between the medial brows (Fig. 5). The person appears hostile, angry or depressed. The negative effect of this subconscious body language is felt by both men and women but particularly women.[60-63]

Our standard technique is to inject with the patient sitting. A tuberculin syringe is loaded with botulinum A toxin (20 to 25 units for women with fine lines, 30

to 35 units for men or for women with deeper lines). Prechilling the area to be injected usually prevents the minimal discomfort associated with the injection and is helpful in preventing bruising in people taking ASA or nonsteroidal anti-inflammatory drugs (NSAIDs). We avoid the use of local anesthesia because the injections are more painful than the toxin injections and because the increased volume would cause unwanted diffusion of unbound toxin, increasing the likelihood of ptosis.

The first injection is made just above the medial eyebrow, in line with the inner canthus. The thumb is placed under the belly of the corrugator, posteroinferior to the medial eyebrow. The needle (1.3-cm 30-gauge) is passed posteroinferiorly into the muscle, and 4 to 5 units are injected. After partial withdrawal, the needle is advanced directly posteriorly into the orbicularis, and a further 4 to 5 units are injected. The needle is then withdrawn, and gentle direct pressure is placed over the penetration site. The injection is repeated on the other side.

We always treat the procerus. If this muscle is not treated, the patient will return with a "procerus line" between the brows at the root of the nose. Just above the intersection of imaginary lines drawn on both sides from the medial brow to the opposite medial canthus, 5 units are injected.

For patients with larger corrugator–orbicularis complexes we also inject 5 units 10 mm above the eyebrow in the midpupillary line. This is done only when needed; otherwise it will cause a reduction in the expressiveness of the lateral brow area and may produce lateral brow ptosis.

Most patients greatly appreciate the resulting smoothness of the glabellar region (Fig. 5). In some patients muscular headaches are also alleviated. Denervating the brow every 3 to 4 months for approximately 18 months results in a biofeedback-type response. The patient stops recruiting the frowning muscles and then requires retreatment only about once a year.

Complications

Complications have been minimal. The most important complication is ptosis due to transient paresis of the levator palpebrae superioris. In our experience this follows 1% to 2% of injection sessions,[60,61] is usually minimal (1 to 2 mm) and lasts for about 3 to 4 weeks. To help avoid this complication a low injection volume (1 mL of saline/100 units) should be used, and the injection should be given accurately and never into or below the brow lateral to the inner canthus. In addition, patients should be instructed to avoid manipulating the injected areas with their hands for 2 to 3 hours after injection, to remain vertical for 3 to 4 hours after injection, and to frown and grimace in the first 2 to 3 hours after injection because the toxin is preferentially taken up by actively contracting muscles.

Before injection we always ascertain whether the patient bruises easily, bleeds excessively on tooth extraction or is taking platelet inhibitors, such as ASA or NSAIDs. These patients require pressure over the injection sites for several minutes as well as application of an ice pack before and after injection. Occasionally a patient experiences mild pain at the injection sites or a tension headache for a few hours after injection.

Crow's-feet

A fan of straight lines radiating from the outer canthus may be present only when smiling or also at rest (Fig. 6). Weakening the orbicularis oculi temporal to the lateral orbital wall reduces these lines[60,61,64] (Fig. 6) and can be used as an adjunct to upper and lower blepharoplasty or carbon dioxide laser resurfacing.

Our technique is to inject just posterior to the lateral orbital wall, where one sees the most lines when the patient forces a smile, 1 cm above and 1 cm below. The inferior injection can be 1 unit or so smaller than the other two injections to lessen any paresis of the temporal orbicularis and a "round eye" contour change to the palpebral aperture. A total of 2 to 5 units are injected in each site. There is no need to achieve total focal denervation: the advantage of botulinum toxin is that the response can be graduated according to the individual patient's needs. After the first injection session the patient will make further decisions about treatment. The effect usually lasts for 4 to 6 months.

Horizontal forehead lines

Patients with ptosis masking poor levator function with frontalis action will have a poor cosmetic result with botulinum toxin treatment. They require ptosis repair. Patients with excessive frontalis tone to compensate for brow ptosis require brow-lift surgery.

The importance of the dynamic action of the frontalis is demonstrated after treatment of the glabel-

Fig. 6—Left: Pretreatment appearance of crow's-feet with patient smiling. One week after treatment of temporal orbicularis oculi, crow's-feet were softened with patient's face at rest and smiling (right).

lar area with botulinum toxin. Paralysis of the depressor supercilii, corrugator and procerus allows unopposed action of the frontalis, producing a medial brow lift of 1 to 2 mm.[60,61]

We frequently further dilute the toxin since spread of the toxin is desirable in this area. In women a single 10-unit injection into the forehead will produce a circular area of paralysis 3 cm in diameter. We inject 1 to 2 units every 1 to 2 cm along either side of a deep forehead crease for its central two-thirds, observing the response over the next 4 to 6 weeks (Fig. 7). Many patients do not like to lose the ability to elevate one brow or the other laterally, so it is prudent to start centrally and let the patient judge whether he or she is ready for full brow denervation.

Facial asymmetry

Facial asymmetry results from Bell's palsy and hemifacial spasm and after cosmetic surgery. Botulinum toxin treatment of the normal but relatively hyperfunctional side restores facial symmetry.[65]

Eyelid–upper lip synkinesis

After face-lift surgery, eyelid closure may produce an involuntary contraction of the ipsilateral upper lip levators, giving a sneering expression that is upsetting for the patient. Under electromyographic control, it is possible to inject exactly the co-contracting muscles, producing relief from this complication.[66]

Fig. 7—Left: Appearance of horizontal forehead lines with patient contracting frontalis, before toxin has taken effect. Two days after treatment, lines were softened at rest and in action (right). There is no induced brow ptosis.

Reversal of overcorrection on brow lift

Some patients are unhappy with the extremely high hairline seen after coronal brow lift, particularly if it is asymmetric. Injection of botulinum toxin into the frontalis relaxes the brow height and restores symmetry, an effect that might not be expected because of the presumed periosteal attachments of the elevated forehead.

ELECTROMYOGRAPHIC CONTROL

Electromyography is useful in the treatment of muscles with single motor end plates, such as extraocular muscles treated for strabismus or nystagmus, in the retreatment of incompletely treated muscle groups (e.g., brow furrows) and for isolating synkinetic muscles. For most patients with blepharospasm or hemifacial spasm and those undergoing cosmetic treatments the procedure is not necessary because the subcutaneous muscular aponeurotic system allows the underlying muscular contraction to be seen in the dynamic formation of facial wrinkles.

The machine we use is available from Allergan Inc. and is relatively simple. Motor end plate recruitment is heard as an amplified roar from the speaker. Allergan provides Teflon-coated needles so that the muscular activity heard is from the tip of the needle only; injection through the hollow recording needle ensures accuracy in toxin placement.

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The Botulinum Toxin treatment of lower facial muscles in patients affected by hemifacial spasm

Eleopra R., Tugnoli V., *Marchese Ragona R, **De Grandis D
Neurological Departments of Ferrara and **Rovigo, Italy
*Othorinolaringology Department of Ferrara, Italy

The symptomatic relief of hemifacial spasm (HS) by using Botulinum Toxin (BoNT) is well known. Nevertheless the treatment of lower facial muscles (LFM) is still debated for the frequent adverse effects. No data have been reported about the clinical results after selective LFM injections. We have analysed the results of selective BoNT injections in LFM, with the aim to detect the better combination for good clinical results. A videotape recording and the degree of HS scored on a 0 to 4 scale were performed in 59 patients with HS before and after BonT/A treatment. The choice of LFM was made on the basis of clinical evaluation, with particular care to the antagonism between single muscle groups such as orbicularis oris muscle and levator labii aleque nasii, levator labii superioris, zygomaticus, buccinator, mentalis, depressor labii inferioris. Low mean dosages of American (BOTOX) (3 to 12 I.U.) and English (DYSPORT) (10 to 50 I.U.) BoNT/A were administered in 2 to 4 points for each muscle. Buccinator in deep layers was treated by endoral injections without EMG control and compared with traditional superficial approach. Clinical effects divided in good, adverse and none effects were reported for each muscle. Levator labii aleque nasii, zygomaticus and buccinator treatment was well tolerated, without significant side effects. Excessive lip downfall was observed after levator labii superioris injection for a long period. The isolated administration in mentalis and orbicularis oris determined frequently eating and speaking impairment. The endoral injections were simple and well tolerated.Our data suggest that the treatment of single LFM in HF patients is useful if the approach is differentiated for each patients on the basis of clinical evaluation, with particular care in avoiding critical sites.